INTERVIEW SUMMARY

The Applicants would like to thank the Examiner for her telephone call of September 30, 2004. The Examiner and Vita Conforti briefly discussed the Applicants providing comments on the Declaration by Dr. Robert F. Graziano.

REMARKS

The Examiner requested comments from the Applicants regarding "whether the anti-CD30 antibodies of HRS-4, and Ber-H2 would inhibit Hodgkin's Disease cell line cells as shown at Figure 1A-B of the attached "Declaration by Dr. Robert F. Graziano"." The Applicants will address the Examiner's specific question. Additionally, the Applicants will address the appropriateness of the Protest filed on April 16, 2004 and the Protester's allegations of lack of enablement and lack of novelty.

1. **The Protest filed April 16, 2004 is improper and should not be considered**

The Applicants would like to thank the Examiner for her efforts in reviewing the Protests filed herein. However, the Applicants assert that the Protest filed on April 16, 2004 is improper and should not be considered. The Protest filed on April 16, 2004 is improper because the Protester did not (1) submit additional prior art nor (2) raise new issues which could not have been earlier presented.

"[I]nitial protests should be as complete as possible when first filed." MPEP 1901.07. "Under 37 CFR 1.291 (c), protestor participation ends with the filing of the initial protest, and protestor will not be allowed to complete any protest that is incomplete." MPEP 1901.07(a). Further, "[n]o further submission on behalf of protestor will be considered, except for additional prior art, or unless such submission clearly raises new issues which could not have been earlier presented." MPEP 1901.07(a). (emphasis added). In the instant application, the Protester filed two Protests: the first on March 3, 2003 ("first Protest") and the second on April 16, 2004 ("second Protest"). In the second Protest, the Protester submitted Falini *et al*, 1992, Brit. J. Haematology 82:38-45 and a Declaration by Dr. Robert F. Graziano.

a. **The Protester did not submit additional prior art**

Falini *et al* is not additional prior art. Applicants submitted Falini *et al* to the United States Patent and Trademark Office (USPTO) in an Information Disclosure Statement (IDS) as reference AL dated June 4, 2001. Falini *et al* has been available to

the Examiner for 34 months prior to its submission by the Protester. The Protester was aware of its submission by review of the image file wrapper available at the USPTO web page under Public PAIR as "List of References Cited by Applicant" dated July 18, 2001 prior to the date of the submission of the second Protest. Public PAIR shows the signed and dated by the Examiner "List of References Cited" sheets accompanying the IDS dated June 4, 2001. Since Falini *et al* was already cited as art in the instant application, it is not additional prior art.

b. The second Protest does not raise new issues which could not have been earlier presented

The Declaration by Dr. Graziano does not raise new issues which could not have been earlier presented. MPEP 1901.07 and 1901.07(a) state that protests should be as complete as possible when first filed and incomplete protests should *not* be allowed to be completed. Applicants assert that the materials and methods used in the studies described in Dr. Graziano's declaration were available to him prior to the filing of the first Protest. Protester has not put forth any reason why Dr. Graziano's declaration could not have been previously presented. Protester merely states that the data "had not been generated at the time of the initial Protest." Second Protest, page 1, lines 1-3. This does not meet the standard of submitting a complete protest *ab initio*. Protesters are attempting to get a "second bite at the apple." Clearly, Falini *et al* has been available since at least June 4, 2001, *i.e.* prior to the filing of the first Protest. Further, Applicants allege that the materials to conduct Dr. Graziano's studies were available to him prior to the filing of the first Protest. For example, Ber-H2 is commercially available from at least the DakoCytomation catalog, Carpinteria, CA, available at www dakocytomation.us. Any allegations of lack of enablement based on the alleged lack of correlation between Falini *et al* and the studies described in the Declaration of Dr. Graziano could have been filed with the filing of the first Protest. Contrary to the directions of the statute, the Protester chose to not file a protest "as complete as possible when first filed." MPEP 1901.07. As such, the second Protest does not raise new issues which could not have been earlier presented.

c. The Protester should not be allowed to continue their participation in the examination of the instant application

Applicants respectfully assert that the Examiner should not allow the Protester to continue their involvement in the instant application. According to 37 CFR 1.291(c), Applicants assert that the Protester's participation should have ended with the filing of the first Protest. Paragraph 1901.06 of the MPEP discusses the completeness of Protest as follows:

> A protestor may not complete an incomplete protest, nor further participate in, or inquire as to the status of, any Office proceedings relating to the initial protest. 37 CFR 1.291. The examiner must not, therefore, communicate with protestor in any way and will not consider a later submission by protestor, except for additional prior art, or unless such submission raises new issues which could not have been earlier raised and constitutes in effect a new protest (see MPEP § 1901.07). Improper protests will be returned by the TC Director.

Applicants respectfully assert that the Examiner should not consider the second Protest and the accompanying Declaration of Dr. Graziano.

2. Studies regarding inhibition of Hodgkin's Disease cell line cells with antibodies HRS-4 and Ber-H2

With regards to the specific question raised by the Examiner regarding whether the anti-CD30 antibodies of HRS-4 and Ber-H2 would inhibit Hodgkin's Disease cell line cells, the Applicants provide as evidence the Declaration of Kerry Klussman ("Klussman Declaration") (attached hereto as Exhibit A).

a. The Klussman Declaration provides evidence that Ber-H2 does not inhibit Hodgkin's Disease (HD) cell line cells

Under the direction of the inventors in the current application, Ms. Klussman conducted *in vitro* studies in February 2000 using the conditions described in Example 6, pages 50-52, of the current application. She tested an anti-CD30 antibody, referred to as Ber-H2, in the soluble and immobilized assays described in the current application using the following cell lines: L540 (Hodgkin's lymphoma derived cell line with a T cell phenotype) (pg 50, line 6 of the application) and L428 (Hodgkin's lymphoma derived cell line with a B cell phenotype) (pg 50, line 7 of the application). (para. 15, Klussman

Declaration). She cultured the L540 and L428 cells in flat-bottom, 96 well plates at a density of 50,000 or 5,000 cells/well in growth media RPMI with 10% fetal bovine serum (FBS) for cell line L428 and RPMI/20% FBS for cell line L540. (pg 50, lines 19-24 of the application; para. 15, Klussman Declaration). To evaluate the biological activity, she cultured the CD30-expressing HD cell lines (either 50,000 cells/well or 5,000 cells/well) in the presence of soluble or immobilized Ber-H2, AC10 and He-Fi-1 antibodies and a third prior art anti-CD30 antibody (as a control) referred to as Ki-1 (previously shown to have no effect on HD cell lines, Gruss *et al.*, 1996, Blood 83:2045-2056). (pg 51, lines 1-15 of the application; para. 16, Klussman Declaration).

As shown in Figures 1a-b and 2a-b, Exhibits to Ms. Klussman's Declaration, neither immobilized nor soluble Ber-H2 had cytotoxic effects on the HD cell lines L428 and L540. (para. 17, Klussman Declaration). The data confirms that the prior art antibodies Ki-1 and Ber-H2 do not exert a cytostatic or cytotoxic effect on HD cell lines. (para. 18, Klussman Declaration). At least Example 6, pages 50-52, of the current application provides the conditions for conducting assays for antibodies having the properties of immunospecifically binding CD30 and exerting a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein the antibodies exert the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent and in the absence of cells other than cells of said Hodgkin's Disease cell line. (*See* at least pg 51, lines 1-15 of the application; para. 19, Klussman Declaration).

b. The claims of the instant application are enabled

The specification of the application enables the instant claims. The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A

Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.
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> *Id.* at 219 (emphasis in the original).

Further, in the application of the law of enablement to antibody-related inventions, the Examiner's attention is directed to *In re Wands*, 858 F.2d 731, 8 USPQ2d

1400 (Fed. Cir. 1988), in which the Federal Circuit reversed a Patent Office rejection of claims directed to immunoassays of hepatitis B surface antigen using high affinity monoclonal IgM antibodies for lack of enablement. The court concluded that, even without a hybridoma deposit, undue experimentation would not be required to practice the invention. In arriving at its decision, the court noted that the finding of enablement was "consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980." *Wands*, 858 F.2d at 736, citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94.

With regards to inoperative embodiments, as discussed in MPEP paragraph 2164.08(b),

> [t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

Typically, inoperative embodiments are excluded by language in a claim (e.g., preamble). MPEP 2164.08(b).

In the instant situation, the Klussman Declaration confirms that the application enables the instant claims. Ms. Klussman conducted experiments in February 2000 with Ber-H2 according to the teachings of the application. Her experiments showed a lack of *in vitro* activity of Ber-H2. In accordance with the disclosure of the instant application, her experiments also showed *in vitro* activity of AC10 and HeFi-1. The results of Ms. Klussman's experiments showing a lack of activity of Ber-H2 *in vitro* correlates with the *in vivo* data of Falini *et al.* As confirmed by the working Examples in the application and the experiments described in the Klussman Declaration, the application teaches one of skill in the art, without undue experimentation, how to select an antibody or protein having the properties of immunospecifically binding CD30 and exerting a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein the antibodies exert the

cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent and in the absence of cells other than cells of said Hodgkin's Disease cell line. Therefore, the claims are enabled.

The Protester admits that the scope of the claims "...may encompass inoperable embodiments...". (Second Protest, page 6, line 13). The Protester alleges that "...the claims of the '406 cannot be found to properly satisfy 35 USC 112, first paragraph, because there is insufficient guidance in the specification for selecting anti-CD30 antibodies having the claimed *in vivo* therapeutic property." (Second Protest, page 6, lines 10-13). However, the Klussman Declaration provides evidence to the contrary. Using the conditions described in the application, in the experiment described with Ber-H2 discussed above, she was able to show that Ber-H2 had a lack of *in vitro* activity. As discussed in the MPEP 2164.08(b), the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. In the instant case, a person of skill in the art could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.

c. The Declaration of Dr. Graziano cannot be used to challenge the enablement of the claims

Additionally, the Applicants assert that the Declaration of Dr. Graziano discussing the studies he conducted cannot be used to challenge the enablement of the instant claims. "A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed." John Hopkins University v. CellPro Inc., 152 F.3rd 1342, 1360, 47 USPQ2d 1705, 1718 (Fed. Cir. 1998). In *John Hopkins*, CellPro's expert, Dr. Sutherland, deviated from the teachings of the patent in his attempt to make an antibody covered by the patent claims. The Federal Circuit held that "[b]ecause Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law." Likewise, Dr. Graziano deviated from the teachings of the patent application in his attempts to select an antibody having the claimed properties. (para. 13, Klussman Declaration). As discussed in paragraph 10 of the Declaration of Kerry Klussman, Dr. Graziano's studies differed from the

conditions disclosed in the application (pg 50, lines 25-30 of the instant application) at least by the:

a. amount of secondary cross linking antibody (3 µg/ml used by Dr. Graziano vs. 20 µg/ml used in the Example),
b. concentration of cells used by Dr. Graziano is unknown (50,000 or 5,000 cells/well in the Example),
c. incubation time (96 hours by Dr. Graziano vs. 72 hours in the Example), and
d. amount of ^{3}H-thymidine (0.5 µCi/well used by Dr. Graziano vs. 1 µCi/well for the final 5 hours in the Example).

As such, the Declaration of Dr. Graziano is insufficient to disprove enablement.

Further, in *John Hopkins*, CellPro asserted the declaration of one of its experts, Dr. John Wijdenes, in an attempt to prove that the amount of experimentation needed to successfully practice the invention disclosed in the patent at issue was undue. Although Dr. Wijdenes concluded that it was generally "more difficult" for him to produce an antibody which would fall under the claims of the patent there at issue, he did not attribute this difficulty to any shortcomings in the disclosure of the patent at issue. Instead, Dr. Wijdenes's declaration suggested that the Kohler/Milstein technique was not foolproof, and that success with this technique commonly required repetition. The lack of certainty was thus not attributable to a failure of disclosure in the patent at issue. The court stated that:

> [s]uch routine experimentation does not constitute undue experimentation:
>
> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

John Hopkins University v. CellPro Inc., 152 F.3rd 1342, 1360-61, 47 USPQ2d 1705, 1718-19 (Fed. Cir. 1998). Likewise, in the instant application, Dr. Graziano states that he

allegedly followed the conditions set forth in the application to conduct his experiments. He does not attribute his supposed lack of correlation between his *in vitro* studies and Falini *et al*'s *in vivo* conclusions to any shortcomings in the disclosure of the instant application.

3. **Pohl *et al* does not anticipate the claims**

Protesters allege that Pohl *et al.*, 1993, Int. J. Cancer 54:418-425 anticipate the claims. Applicant respectfully traverses.

The Applicants assert that Pohl *et al.*, 1993, Int. J. Cancer 54:418-425 do not anticipate the claims. For a reference to anticipate a claim, it must *clearly and unequivocally disclose*, not merely suggest each and every element of the claimed invention as arranged in the claims. *See Idacon v. Central Forrest Products, 3 USPQ 2d 1079, 1083* (emphasis added). "A claim is anticipated only if each and every element ... is found in a single prior art reference." MPEP 2131. A reference must be cited for what it fairly teaches. *In re Burkel*, 201 U.S.P.Q. 67 (C.C.P.A. 1979). Contrary to the conclusion of Dr. Graziano in para. 4 of his declaration, Pohl *et al.* do not describe the *in vivo* use of HRS-4 to treat Hodgkin's Disease in animal models. (para. 6, Klussman Declaration). On page 422, right side column titled *Prevention of Tumor Growth in vivo by Ab3 4A4*, Pohl *et al* tested the ability of Ab3 4A4 to prevent tumor growth *in vivo*. (para. 6, Klussman Declaration). Pohl *et al* describe the pretreatment of SCID mice with HRS-4. (Pohl *et al.*, page 422, right hand column, first full paragraph). One hour subsequent to pretreatment with HRS-4, the SCID mice were subcutaneously injected with a number of L540 tumor cells. (para. 6, Klussman Declaration). Pohl *et al* do not describe a study where SCID mice with established tumors were treated with HRS-4. (para. 6, Klussman Declaration). As attested to by Ms. Klussman in paragraphs 5 and 6 of her declaration, Pohl *et al* do not describe a "method for the treatment of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment" an antibody or protein as claimed in claims 1, 8, and 11 of the instant application. Since Pohl *et al* do not teach every element of independent claims 1, 8 and 11, Pohl *et al* cannot anticipate claims 1, 8, and 11 nor any claims dependant therefrom.

CONCLUSION

Applicants respectfully request that the remarks of the present Communication be entered and made of record in the instant application. Applicants respectfully request an early Notice of Allowance.

Applicants request that the Examiner call the undersigned attorney at (425) 527-4122 if any questions or issues remain.

Respectfully submitted,

Vita G. Conforti
Registration No. 39,639
Attorney for Applicants

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SEATTLE GENETICS, INC.
21823 30th Drive SE
Bothell, Washington 98021
Telephone: (425) 527-4122
Fax: (425) 527-4123